CHEST

Prostanoids in Asthma and COPD

Actions, Dysregulation, and Therapeutic Opportunities

Zbigniew Zaslona, PhD; and Marc Peters-Golden, MD

Pathophysiologic gaps in the actions of currently available treatments for asthma and COPD include neutrophilic inflammation, airway remodeling, and alveolar destruction. All of these processes can be modulated by cyclic adenosine monophosphate-elevating prostaglandins E_2 and I_2 (also known as prostacyclin). These prostanoids have long been known to elicit bronchodilation and to protect against bronchoconstriction provoked by a variety of stimuli. Much less well known is their capacity to inhibit inflammatory responses involving activation of lymphocytes, eosinophils, and neutrophils, as well as to attenuate epithelial injury and mesenchymal cell activation. This profile of actions identifies prostanoids as attractive candidates for exogenous administration in asthma. By contrast, excessive prostanoid production and signaling might contribute to both the increased susceptibility to infections that drive COPD exacerbations and the inadequate alveolar repair that characterizes emphysema. Inhibition of endogenous prostanoid synthesis or signaling, thus, has therapeutic potential for these types of patients. By virtue of their pleiotropic capacity to modulate numerous pathophysiologic processes relevant to the expression and natural history of airway diseases, prostanoids emerge as attractive targets for therapeutic manipulation. CHEST 2015; 148(5):1300-1306

ABBREVIATIONS: cAMP = cyclic adenosine monophosphate; COX = cyclooxygenase; EP = E prostanoid receptor; Epac = exchange protein activated by cyclic adenosine monophosphate; GPCR = G protein-coupled receptor; IP = I prostanoid receptor; PG = prostaglandin; PKA = protein kinase A; Th = T-helper

Asthma and COPD represent the two most common chronic lung diseases. Although both are characterized by airflow obstruction and treated with bronchodilators and corticosteroids, they differ substantially in etiology, pathophysiology, and natural history. Despite numerous advances in management of these disorders over the past 2 decades, disease burden remains high and unmet needs are apparent. For example, no current treatment approaches effectively ameliorate neutrophilic inflammation, airway remodeling, or alveolar destruction. Although drug development increasingly favors therapies designed to block specific molecular targets, strategies that are capable of targeting multiple pathophysiologic components of obstructive lung diseases still command appeal.

This article focuses on two specific prostanoid lipid mediators—prostaglandin (PG)

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AFFILIATIONS: From the Division of Pulmonary and Critical Care Medicine, University of Michigan Health System, Ann Arbor, MI.

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CORRESPONDENCE TO: Marc Peters-Golden, MD, 6301 MSRB III, 1150 W Medical Center Dr, Ann Arbor, MI 48109-5642; e-mail: petersm@umich.edu

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E_2 and PGI_2 (also known as prostacyclin)—that exert pleiotropic effects on lung structure and function, as well as on immune and inflammatory processes. We review available evidence suggesting that these endogenous mediators are deregulated in airway disease and that therapeutic strategies involving either their administration or inhibition may have utility in asthma and COPD. We will not consider other prostanoids, such as PGD_2 and thromboxane A_2, but interested readers are referred to an article[1] that more comprehensively reviews the pertinent airway actions of all prostanoids than space permits here.

Prostanoid Synthesis, Receptors, and Signaling

Prostanoids are a family of metabolites of the fatty acid arachidonic acid, which include PGD_2, PGE_2, $PGF_{2\alpha}$, and PGI_2, as well as thromboxane A_2.[2] Their synthesis entails hydrolysis of arachidonic acid from membrane phospholipids by phospholipase A_2, its oxygenation by constitutive cyclooxygenase (COX)-1 and inducible COX-2 isoforms, and isomerization by specific terminal synthases (Fig 1). PGE_2 is produced by virtually all lung cell types, but the most abundant sources are epithelial cells, fibroblasts, and macrophages.[3] The major source of PGI_2 is endothelial cells.[4]

Prostanoids act in both paracrine and autocrine fashion through G protein-coupled receptors (GPCRs) on the surface of target cells. PGE_2 can bind four distinct GPCRs, E prostanoid (EP) 1-4, while PGI_2 acts via the GPCR I prostanoid receptor (IP). EP2, EP4, and IP are coupled to a stimulatory G_α protein subunit that signals by activating adenylyl cyclase to convert adenosine triphosphate into the second messenger cyclic adenosine monophosphate (cAMP). The β_2 adrenergic receptor, agonists for which have long been a mainstay of therapy for obstructive lung diseases, is also a cAMP-coupled GPCR. cAMP is degraded by phosphodiesterases, and their inhibition by roflumilast represents an alternative means of increasing cAMP.[5] Increased intracellular cAMP levels can be sensed by and activate distinct effectors, the best studied being protein kinase A (PKA) and exchange proteins activated by cAMP (Epacs).[6] PKA acts by phosphorylating diverse target proteins, while Epacs activate the small GTPase Rap1.[6] EP3 is coupled to an inhibitory G_α protein subunit that inhibits adenylyl cyclase activity, resulting in decreased cAMP levels and signaling. EP1 is coupled to $G_{\alpha q}$ subunit, which activates phospholipase C to hydrolyze membrane phospholipids into diacyl glycerol (which activates protein kinase C) and inositol 1,4,5-trisphosphate (which releases calcium from intracellular stores). Therefore, PGE_2 can mediate either suppressive effects (via increased cAMP) or stimulatory effects (via reduced cAMP or increased calcium) on smooth muscle tone and cell activation, depending on the profile of EP receptors expressed on pertinent target cells.

PGE_2 and PGI_2 in Asthma

Asthma is characterized by increased susceptibility to bronchoconstriction and increased mucus secretion, both of which are the consequences of chronic airway inflammation. The inflammation of classic atopic asthma involves antigen sensitization resulting in production of (1) IgE antibodies, which trigger mast cells to secrete mediators such as cysteinyl leukotrienes that reversibly contract airway smooth muscle and (2) type 2 CD4 T-helper (Th) cell-derived cytokines such as IL-4, IL-5, and IL-13, which promote eosinophilic airway inflammation, damage the airway epithelial barrier, and cause mucus gland hyperplasia. Over time, airway smooth-muscle hyperplasia/hypertrophy and subepithelial deposition of extracellular matrix proteins such as collagen can lead to remodeling and irreversible luminal narrowing of the airways. A contrasting paradigm in which airway inflammation is persistently dominated by neutrophils rather than eosinophils is now recognized in a surprisingly large proportion of patients with asthma.[7] This undoubtedly contributes to the unexpectedly high frequency of corticosteroid resistance among these patients,[8] as neutrophilic inflammation is notoriously refractory to the actions of these agents.

Over a 50-year span, our appreciation of prostanoid actions in the airways has evolved from mere regulators of airway tone to molecules influencing virtually every aspect of structural and inflammatory cell biology. Inhalation of exogenous PGE_2 or its analogs has long been known to result in bronchodilation as well as protection against early- and late-phase bronchoconstriction induced by various triggers in people with asthma.[9-12] Unfortunately, these beneficial actions are counterbalanced by the fact that inhaled PGE_2 also induces severe cough in animal models and human subjects.[13,14] However, it is now apparent that PGE_2 mediates cough via the EP3 receptor[15] but bronchodilation in humans via EP4,[16] offering the possibility of treatment with a receptor-selective agonist. Limited data reveal that inhalation of a PGI_2 analog in patients with asthma failed to elicit bronchodilation[17,18] but did lower the cough threshold.[19]

Although PGE_2 is classically linked to the cardinal manifestations of inflammation (pain, fever, and swelling), these

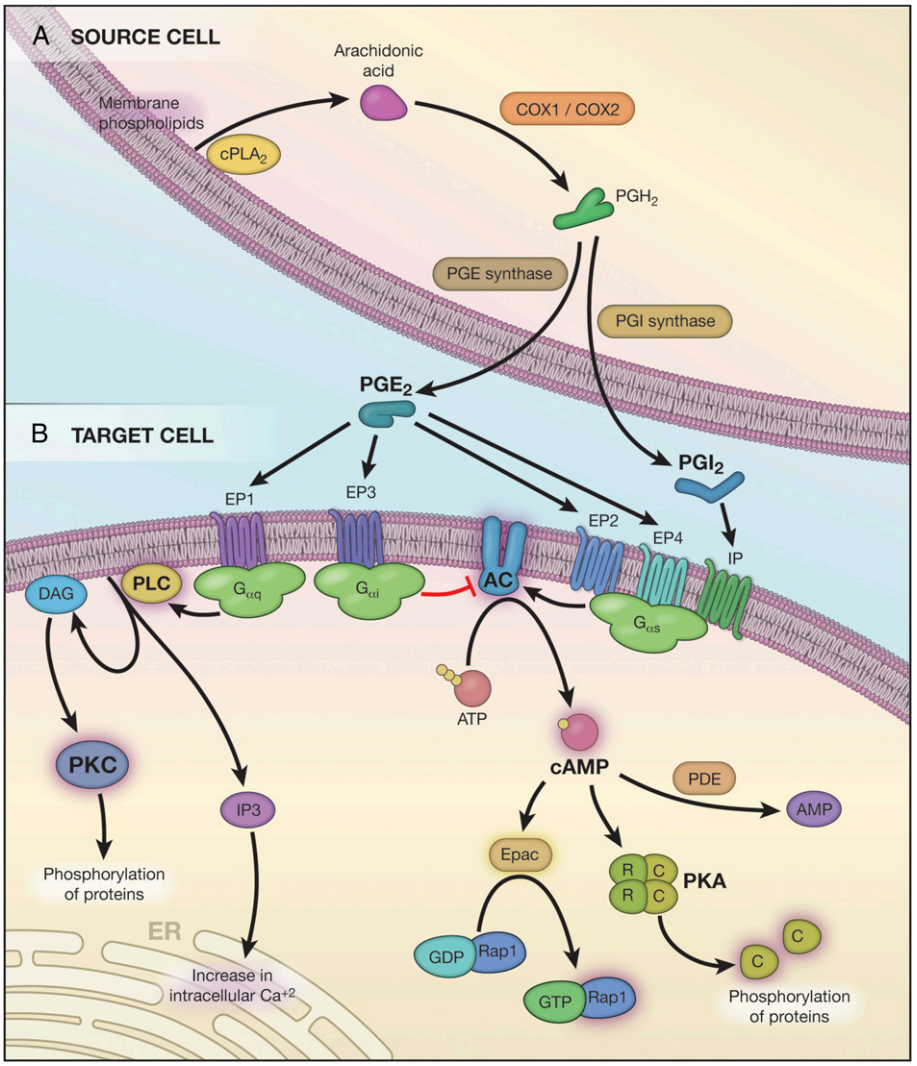

Figure 1 – *Prostanoid synthesis, receptors, and signaling. A, Arachidonic acid is released from membrane phospholipids by $cPLA_2$ and can be metabolized by the constitutive COX-1 or inducible COX-2 enzymes to make PGH_2. Subsequently, PGH_2 serves as substrate for terminal PG synthases, which complete the biosynthesis of specific PG products, including PGE_2 and PGI_2, also known as prostacyclin. These prostanoids can act in both autocrine and paracrine fashion on target cells by binding to cell surface 7-transmembrane G protein-coupled receptors. B, PGE_2 acts through four different receptors (EP1-EP4), while prostacyclin acts via one (IP). EP2, EP4, and IP are coupled to a stimulatory G_α protein subunit, which activates AC. AC catalyzes conversion of ATP to 3′,5′-cAMP, a second messenger in intracellular signaling involved in various biologic processes. The degradation of cAMP into AMP is mediated by PDEs. The prototypic effector for cAMP actions is PKA, a tetramer consisting of two C and two R subunits. Binding of cAMP to R subunits causes their dissociation from C subunits, enabling the release of free C subunits to phosphorylate substrate proteins in the cytosol or nucleus. cAMP can also activate Epacs. Binding of cAMP causes Epacs to catalyze exchange of bound GDP for GTP and, hence, activation of Rap1. EP3 is coupled to an inhibitory G_α subunit, which inhibits the production of cAMP from ATP. EP1 is coupled to a $G_{\alpha q}$ subunit, which activates PLC. PLC catalyzes the formation of DAG and IP3 from phosphatidylinositol. DAG can activate PKC, which can, in turn, phosphorylate target proteins. IP3 translocates to the ER, where it triggers an increase in intracellular Ca^{2+} and activates numerous signaling events. AC = adenylyl cyclase; ATP = adenosine triphosphate; C = catalytic; Ca^{2+} = calcium; cAMP = cyclic adenosine monophosphate; COX = cyclooxygenase; $cPLA_2$ = cytosolic phospholipase A_2; DAG = diacylglycerol; EP = E prostanoid receptor; Epac = exhange protein activated by cyclic adenosine monophosphate; ER = endoplasmic reticulum; GDP = guanosine diphosphate; GTP = guanosine triphosphate; IP = I prostanoid receptor; IP3 = inositol 1,4,5-trisphosphate; PDE = phosphodiesterase; PG = prostaglandin; PGH_2 = prostaglandin H_2; PKA = protein kinase A; PKC = protein kinase C; PLC = phospholipase C; R = regulatory; Rap1 = Ras-related protein 1.*

effects reflect its actions on nerves, the hypothalamus, and the microvasculature, respectively, rather than on leukocytes. In fact, its direct effects on inflammatory cell functions are overwhelmingly inhibitory, and such effects have been validated in mouse models of allergic asthma. These leukocyte suppressive actions of PGE_2 are invariably mediated by increased intracellular cAMP (via EP2 > EP4 activation), and many are shared by PGI_2-IP signaling. Pertinent such actions of PGE_2 and/or PGI_2 include inhibition of mast cell secretory responses,[20] trafficking of neutrophils[21] and eosinophils,[22] dendritic cell activation or function,[23,24] and cytokine generation and proliferation by both type 1 Th cell and type 2 Th cell subsets of T lymphocytes[24-26]; these are

summarized in Table 1.[15,19,20,22,23,25-41] Interestingly, PGE_2 also promotes the differentiation and function of regulatory T cells, which restrain immune responses.[34] Potentially pro-inflammatory actions of these prostanoids include their ability to promote (1) IgE production by B cells[35]; (2) type 17 Th cell differentiation,[28,32] which would be expected to enhance neutrophilic inflammation (which, however, might be counteracted by their inhibition of cell trafficking); and (3) dendritic cell maturation.[28] Consistent with its net antiinflammatory actions, inhaled PGE_2 also attenuates levels of eosinophils[42] and PGD_2[43] in the airways of allergen-challenged patients with asthma.

Prostanoids also exert salutary actions on various aspects of airway remodeling (Table 1). For example, PGE_2 promotes airway epithelial cell wound closure[36] while inhibiting proliferation of airway[39] and vascular[40] smooth muscle cells. PGE_2 also inhibits survival,[44] proliferation,[45] collagen synthesis,[37] and myofibroblast differentiation[46] in lung fibroblasts. PGI_2 likewise inhibits fibroblast functions[38] in vitro and airway remodeling in asthma models in vivo.[47] The effects of prostanoids on lower airway mucus secretion are poorly understood, but PGE_2 has been reported to inhibit allergen-induced mucus hypersecretion in nasal epithelium of sensitized rats.[48]

The bronchoprotective function of endogenous prostanoids is illustrated by the syndrome of aspirin-exacerbated respiratory disease, also known as aspirin-induced asthma, which occurs in 5% to 10% of people with asthma.[49] In these susceptible patients, ingestion of aspirin or other COX-1 inhibitors unleashes a marked activation of mast cells and eosinophils. COX-1 inhibitors likewise augment type 2 Th cell responses and features of allergic inflammation when administered during antigen sensitization in murine models.[50] COX inhibition does not distinguish among various candidate protective prostanoids, but studies with specific receptor-deficient mice support the potential contributions of both PGE_2-EP2[25] and PGI_2-IP[29] signaling as brakes on inflammation. Support for disruption of the PGE_2-EP2 brake as a basis for human aspirin-exacerbated respiratory disease derives from observations that airway tissue from these patients exhibits deficiencies in both PGE_2 levels[51] and EP2 receptor expression,[52] and the association of this syndrome with an EP2 gene polymorphism.[53,54]

PGE_2 and PGI_2 in COPD

COPD is an umbrella term encompassing either of two discrete types of lung response to inhalation of smoke from combusted tobacco or biomass material, or a combination of the two. Chronic bronchitis refers to a primary airway response characterized by mucus hypersecretion and bronchial wall thickening, while emphysema describes a primary parenchymal response characterized by alveolar wall destruction, which results in loss of tethering and secondary collapse of airways. Both forms of COPD involve chronic inflammatory

TABLE 1] Effects of Prostanoids on Various Cell Types Pertinent to Asthma, COPD, or Both

Cell Type	Relevant Disease	Effects of PGE_2-EP2/EP4 Signaling	Effects of PGI_2-IP Signaling
Mast cells	Asthma	↓ (Torres et al[20], Säfholm et al[27])	↓?
Dendritic cells	Asthma/COPD	↓↑ (Kalinski[28])	↓ (Idzko et al[23])
Neutrophils	Asthma/COPD	↓ (Mizuno et al[21])	↓ (Mizuno et al[21])
Eosinophils	Asthma	↓ (Sturm et al[22])	↓ (Zhou et al[29])
Macrophages	Asthma/COPD	↓ (Aronoff et al[30])	↓ (Aronoff et al[31])
Th1 cells	COPD	↓ (Kalinski[28])	↓ (Zhou et al[26])
Th2 cells	Asthma	↓ (Zaslona et al[25])	↓ (Zhou et al[26])
Th17 cells	Asthma/COPD	↑ (Kalinski[28])	↑ (Zhou et al[32])
CD8 T cells	COPD	↓ (Ahmadi et al[33])	?
T regulatory cells	Asthma/COPD	↑ (Baratelli et al[34])	?
B cells/IgE	Asthma	↑ (Fedyk and Phipps[35])	?
Epithelial cells	Asthma/COPD	↑ (Savla et al[36])	?
Fibroblasts	Asthma/COPD	↓ (Liu et al[37])	↓ (Kohyama et al[38])
Smooth muscle cells	Asthma	↓ (Mori et al[39], Lundequist et al[40])	↓ (Jain et al[41])
Airway sensory nerves	Asthma/COPD	ne (Maher et al[15])	↑ (Ishiura et al[19])

↑ = activation; ↓ = inhibition; ↓↑ = activation and inhibition of distinct functions; ne = no effect; EP = E prostanoid receptor; IP = I prostanoid receptor; PG = prostaglandin; ? = effect unknown; Th = T-helper.

processes driven primarily by expanded populations of activated macrophages, neutrophils, and lymphocytes (particularly CD8 T cells), all of which elaborate inflammatory mediators, oxidants, and proteases.[55] COPD is also characterized by accelerated senescence of fibroblasts,[56] and the accompanying deficiency of parenchymal extracellular matrix in emphysema has been termed "mesenchymal insufficiency."[57]

In contrast to what has been observed in patients with asthma,[58] PGE_2 levels are increased in respiratory secretions from patients with COPD.[59,60] Increased PGE_2-EP2/4 signaling has also been observed in fibroblasts isolated from the lung parenchyma of patients with emphysematous COPD, reflecting overexpression of COX-1 and -2[61] as well as EP2/4 receptors.[56] Interestingly, this overexpression profile of COX-2/EP2 is the inverse of the deficiency profile found in fibroblasts from patients with idiopathic pulmonary fibrosis,[45,62] a condition characterized by "mesenchymal excess." Fibroblasts from patients with COPD likewise synthesize higher levels of PGI_2 than do control cells.[63]

In view of their ability to promote fibroblast senescence[56] and to broadly inhibit fibroblast survival and activation, increased PGE_2 and/or PGI_2 signaling could contribute to the impaired lung repair[61] and the alveolar destruction of emphysema. This provides a rationale for a therapeutic strategy consisting of inhibition of prostanoid synthesis and/or antagonism of EP2/4 or IP receptors. Indeed, an ongoing US National Institutes of Health-supported randomized proof-of-concept trial[64] will determine the ability of the COX inhibitor ibuprofen (as compared with placebo) to improve biochemical measures of lung repair in the distal lung of patients with emphysema. It should be noted, however, that such a strategy is in apparent conflict with the observation that administration of a stable PGI_2 analog protected against cigarette smoke extract-induced emphysema in rats.[65] It is pertinent that PGE_2 and PGI_2 also exert broad suppressive actions on innate immune functions of phagocytes,[66,31] so inhibition of their synthesis or receptors might additionally overcome the increased susceptibility to infection that characterizes and contributes to disease exacerbations in COPD. By contrast, the subset of patients with COPD whose clinical phenotype or gene expression profile[67] overlaps that of classic type 2 Th cell-predominant asthma might benefit from EP2/4 or IP agonism.

Conclusions

Based on their capacity to protect against bronchoconstriction, activation of inflammatory cells (including T cells, eosinophils, and neutrophils), and features of airway remodeling, analogs of PGE_2 or PGI_2 have significant appeal for the treatment of asthma as multifaceted therapeutic substances whose repertoire includes critical actions not shared by inhaled corticosteroid/long-acting β agonist—the current gold standard controller agent. A dual EP2/4 agonist would seem to hold the greatest potential as an inhalational agent targeting all of these component processes without eliciting cough. How to best target prostanoid pathways in COPD may be more complicated. A similar approach of exogenous EP2/4 agonism may likewise be useful in patients with COPD whose clinical phenotype overlaps substantially with that of asthma. However, in those with a predominant emphysematous phenotype, inhibition of excessive PGE_2 synthesis (using nonselective COX inhibitors) or signaling (using inhaled or systemic EP2/4 antagonists) might attenuate the mesenchymal insufficiency of this form of disease. A similar approach may boost innate immune function and, thus, be useful in patients who are prone to COPD exacerbation. Maximizing the therapeutic potential inherent in these pathways will require a better understanding of regulation of prostanoid synthesis, receptors, and signaling in the airway vs the parenchymal compartments and among patients with various phenotypes and endotypes of COPD. The possibility that superior pharmacologic precision and, hence, therapeutic specificity and flexibility could be accomplished by bypassing the prostanoid receptors themselves and selectively activating or inhibiting the downstream cAMP effectors PKA or Epac remains entirely unexplored to date.

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